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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,144	06/20/2001	Jurgen Kleinschmidt	03528.0050.CNUS01	6869

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EXAMINER
WINKLER, ULRIKE

ART UNIT	PAPER NUMBER
1648	4

DATE MAILED: 09/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,144	KLEINSCHMIDT ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Specification

The disclosure is objected to because of the following informalities: The margins at the top of the pages are to narrow. In the process of assembling the application file, holes were punched through some of the text found at the top of the page. Applicant is requested to provide a substitute specification in which the margins at the top of the page are increased.

Drawings

Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are rendered indefinite in that they only describe the composition by an arbitrary name "A20". While the name itself may have some notion of activity of the protein or antibody, there is nothing in the claims which distinctly describes the protein or antibody. Placing what appears to be a deposit designation in parenthesis's (DSM ACC2194) does not indicate that "A20" is in fact one and the same as the deposited sample, it merely suggests the A20 may be the same as the DSM ACC2194. Additionally, others in the field may isolate the same protein and give it an entirely different name or others may use the "A20" designation for a completely different compound (see Kim et al. Immunology 1986, abstract). Applicant should particularly point out and distinctly claim the "protein molecule or antibody and variant thereof" by claiming characteristics associated with the protein (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, epitope binding, etc.). Claiming a biochemical molecule by a particular name given to the protein or antibody by the various workers in the field fails to distinctly claim what that protein or antibody is and what the composition is made of.

Claims 1, 2 and 5 contains the trademark/trade name "CNBr-activated sempharose®" and "NHS-activated sempharose®". Where a trademark or trade name is used in a claim as a

limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe activated column matrix and, accordingly, the description is indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is apparent that a specific antibody, A20, is required to practice the claimed invention. As such it must be readily available or obtainable by a repeatable method set forth in the specification, or otherwise known and readily available to the public. If it is not so obtainable or available, the requirements of 35 U.S.C. 112, first paragraph, may be satisfied by an enabling deposit of the antibody. It is noted that the Applicants have deposited the A20 antibody but there is no indication in the specification as to public availability. Therefore, a declaration as to the public availability may be made for enablement purposes.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or statement by an attorney of record over his or her signature and registration number, stating that the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that:

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years. Or 5 years after the last request for the enforceable life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit (see CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimada et al. (WO96/29349) and Wistuba et al. (Journal of Virology, Sept. 1995) and further in view of Harlow (Antibodies, a laboratory manual, 1988). The English language equivalence of the Shimada et al. (WO96/29349) is supplied in order to clarify the rejection because the WO96/29349 is written in Japanese. The English language equivalence of WO96/29349 is U.S. Pat. No. 6,093,534.

The instant invention is directed at purifying and concentrating AAV-2 and antigen portions thereof. This purification is achieved using antibody affinity chromatography, the antibody is crosslinked to the matrix, the specific antibody A20 is used (claim 8), the bound antigen is eluted from the antibody complex with $MgCl_2$ using a concentration range of 0.5-4.5M of $MgCl_2$, the virus is obtained either from a cell extract or from cell supernatants. Additionally, the components are packed into a kit.

Shimada et al. (WO96/29349) teach the production of monoclonal antibodies to AAV, these antibodies can be used for the detection of AAV and for the purification of AAV virus

vectors which can be used in gene therapy. The reference teaches that affinity chromatography techniques are also well known by those skilled in the art. In a typical case, a monoclonal antibody specific to the adeno-associated virus CAP protein is covalently bonded to a solid phase support thus immobilized followed by packing into a column. Then a sample containing the antigen to be purified is poured into the column. Thus the antigen is bonded to the antibody immobilized on the support, while other substances cannot be bonded to the immobilized antibody. After washing the column under appropriate conditions, therefore, the antigen to be purified alone remains in the column. Subsequently, an appropriate eluent is poured into the column so as to loosen the bond between the antigen and the antibody end thus the antigen is eluted to thereby give the purified antigen. The reference does not specifically teach AAV-2 but the techniques are applicable for all AAV viruses that are of interest in human disease and treatment.

Wistuba et al. teach a monoclonal antibody "A20" that is able to recognize AAV-2 CAP proteins and is able to precipitate assembled capsid or portions thereof in immunoprecipitation experiments (page 5312, column 2 and paragraphs 5-7, and figure 6). The reference teaches an affinity purification step in the form of immunoprecipitation, using an antibody directed against the CAP protein. The reference uses protein-A Sepharose beads in the immunoprecipitation. The reference does not teach crosslinking the antibody to an activated cyanogen bromide Sepharose support and the reference does not teach eluting the antigen using $MgCl_2$.

Harlow teaches the use of several matrixes for the use of affinity purification purposes, such as cyanogens bromide activated beads (page 532) the reference also teaches several methods of eluting the antigen from the bound antibody antigen complex (page 551), one of the

gentlest methods is using $MgCl_2$, the concentration range suggested ranges from 3-5 M. The reference does not teach affinity purifying AAV-2 antigen specifically, but it serves as a general guide as to the state of the art at the time the invention was made.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to utilize affinity purification methods as taught Shimada et al. for the purpose of purifying AAV and applying the antibody as taught by Wistuba et al. to purify AAV-2. One having ordinary skill in the art would have been motivated to do this in order to purify commercial level quantities of infectious virus AAV-2 suitable for therapeutic purposes. One having ordinary skill in the art would have reasonable expectation of success utilizing the A20 antibody as taught by Wistuba et al. for the purpose of purification as taught by Shimada et al. because the antibody is directed to the CAP protein as were the antibodies by Shimada et al. AAV-2 is a parvovirus that affects humans and is the virus construct most often used in attempts to transfer genes of interest into human cell lines. It would have been obvious to one of ordinary skill in the art at the time the invention was made optimize the affinity chromatography conditions following the standard art known procedures (Harlow et al.), this includes the choice of solid support and the method of eluting the antigen which is directly dependent on the specific antibody used. Elution conditions must be custom tailored because each antibody will have a different affinity/avidity for the antigen and therefore the optimum conditions must be experimentally established. One having ordinary skill in the art would have been motivated to package the required components into a kit for the sake of conveniently providing the reagents to unskilled personnel. Therefore, the instant invention is obvious over Shimada et al. and Wistuba et al. and further in view of Harlow.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

O'Riordan et al. U.S. Pat. No. 6,143,548, Nov, 2000.

O'Riordan et al. WO97/08298

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D. 9/9/02